UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,974	01/04/2006	Felipe Prosper Cardoso	40140/00701	6945

30636 7590 07/18/2008

FAY KAPLUN & MARCIN, LLP
150 BROADWAY, SUITE 702
NEW YORK, NY 10038

EXAMINER	
SCHUBERG, LAURA J	
ART UNIT	PAPER NUMBER
1657	
MAIL DATE	DELIVERY MODE
07/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,974	PROSPER CARDOSO ET AL.	
	Examiner	Art Unit	
	LAURA SCHUBERG	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-67* is/are pending in the application.

4a) Of the above claim(s) *41-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 31-40) in the reply filed on 04/28/2008 is acknowledged. The traversal is on the ground(s) that the prior art reference, Xia, discloses a different use for the reference composition than the claimed composition as well as a different motivation for the addition of heparin and protamine in the composition. This is not found persuasive because the intended use of the claimed composition only requires that the composition be suitable for the culture of progenitor cells which the Xia media composition is described as being used for. One of ordinary skill in the art of cell culture would have been motivated to lower the concentrations of the ingredients in the Xia media composition in order to conserve resources and save money. Since the common technical feature is the media composition and not the method of using the media composition, the fact that the reference composition has the same ingredients as the claimed composition (page 1134, figure 5, formula C), albeit different concentrations of heparin, suggests that reference media composition is an obvious variant of claimed media composition. Therefore a common technical feature which is an obvious variant of a known composition can not be a special technical feature and thus unity of invention is lacking.

The requirement is still deemed proper and is therefore made FINAL.

Claims 31-67 are pending.

Claims 41-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 31-40 have been examined on the merits.

Specification

The disclosure is objected to because of the following informalities: page 9 paragraphs 53-58 of the disclosure is in Spanish.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 31 recites the limitations of "between 0.1% and 10.000 UI/ml heparin; between 0.1% and 10.000 UI/ml protamine" in lines 4 and 5 of the claim. Since percent values and UI/ml values are different units of concentration the concentration range claimed is unclear what the concentration range of heparin and protamine is suppose to

be and therefore the metes and bounds of the claim are indefinite. In addition, the prior art measures protamine in concentration units of mg/ml which is contrary to Applicant's disclosure of UI/ml and thus the meaning of the claims is unclear.

Claim 31 also recites the limitation "basic nutrients" in line 6 of the claim. Since Applicant's disclosure has not defined what nutrients are considered basic, the metes and bounds of this claim are unclear and thus indefinite.

Claim 39 recites the transitional phrase "further comprising" and then recites additional ingredients that have percentage concentrations that add up to over 100% when added to the composition of claim 31. It is unclear what amounts of the ingredients are included and thus the claim is indefinite. It would appear that Applicant intends for the first 4 ingredients of claim 39 to correspond to ingredients a-d of claim 31 and that the 5th ingredient- penicillin/streptomycin would be a new ingredient added (ingredient e).

Claim 39 recites the limitations of "heparin 0.1 at 100 UI/ml, protamine 0.1 at 100 UI/ml" and claim 40 recites the limitation "0.1 at 250 pg/ml bFGF". It is unclear what amount of the ingredient is included and thus the claims are indefinite. It would appear from Applicant's disclosure (page 4 paragraph 25) that the "at" should be "to" and define a range of concentration for the ingredient in the composition.

Appropriate correction and clarification is required.

Because claims 32-40 depend from indefinite claim 31 and do not clarify the point of confusion, they must also be rejected under 35 U.S.C. 112, second paragraph.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 31-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia et al (The Journal of Immunology,2002).

Claim 31 is drawn to an autologous culture medium of autologous human progenitor stem cells, comprising: a) between 0.1% and 90% of autologous human serum; b) between 0.1 and 10.000 UI/ml heparin; c) between 0.1 and 10.000 UI/nl protamine; and d) a base culture medium including basic nutrients.

Dependent claims include the treatment of the autologous serum, the source of the autologous serum, the method of producing the autologous serum and the inclusion of an antibiotic.

Claims 33-35 are product-by-process claims. M.P.E.P. § 2113 reads, "Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps."

"Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted).

The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979)

The use of 35 U.S.C. §§ 102 and 103 rejections for product-by-process claims has been approved by the courts. "[T]he lack of physical description in a product-by-process claim makes determination of the patentability of the claim more difficult, since in spite of the fact that the claim may recite only process limitations, it is the patentability of the product claimed and not of the recited process steps which must be established. We are therefore of the opinion that when the prior art discloses a product which reasonably appears to be either identical with or only slightly different than a product

claimed in a product-by-process claim, a rejection based alternatively on either section 102 or section 103 of the statute is eminently fair and acceptable. As a practical matter, the Patent Office is not equipped to manufacture products by the myriad of processes put before it and then obtain prior art products and make physical comparisons therewith." *In re Brown*, 459 F.2d 531, 535, 173 USPQ 685, 688 (CCPA 1972).

Xia et al teach a media composition that comprises AIM-V medium containing 2% autologous serum, 25 U/ml heparin and 0.125 mg/ml protamine sulfate (page 1134, figure 5, formula C). The AIM-V media inherently contains the claimed antibiotics streptomycin and gentamycin as well as basic nutrients for cell culture. While the reference is silent with regard to the method of producing the autologous serum, it appears that the claimed autologous serum and the reference autologous serum would be structurally the same. Therefore the limitation of the autologous serum is deemed to be met by the reference. However, even if this were not the case, obtaining autologous human serum from the blood of the patient by means of plasmapheresis is a well established and conventional procedure and therefore obvious. As far as the Examiner can tell, the concentrations of the heparin and the protamine are reasonably close to the claimed concentrations that one of ordinary skill in the art would have been motivated with a reasonable expectation of success to lower the concentration of the heparin or the protamine upon duplicating the experiment of Xia et al in order to conserve resources and lower costs. While the Xia et al reference uses the media composition for a different purpose, as long is there is a motivation and reasonable expectation of success to arrive at the same concentrations as claimed by Applicant, the claimed

composition is obvious. The treating of the autologous serum to inactivate a complement is also obvious as heat inactivation of serum is a well established and conventional procedure in the art of tissue culture (as acknowledged by Applicant on pages 3-4 paragraph 21).

Therefore the teaching of Xia et al renders obvious Applicant's invention as claimed.

Claims 31-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chachques (US 2002/0124855) in view of Furcht et al (US 7,015,037), Duggins (US 4,735,726) and Yang et al (US 6,624,141).

Claim 38 is drawn to the medium of claim 31, further comprising at least one of amphoterycin B and a Fibroblast Growth Factor (FGF).

Claim 39 is drawn to the medium of claim 31, further comprising: 89% HAM-F12; 10% autologous human serum of a patient; heparin 0.1 to 100 UI/ml; protamine 0.1 to 100 UI/ml; and 1% penicillin/streptomycin.

Claim 40 is drawn to the culture medium of claim 39, further comprising at least one of 0.25 mg/ml of amphoterycin B and 0.1 to 250 pg/ml of recombinant bFGF.

Chachques describes a culture medium comprising 79% Ham-F12 medium, 25 pg/ml bFGF, 20% fetal calf serum and 1% penicillin/streptomycin (page 3 para 40). The medium is intended to be used to culture myogenic cells for the repair of a damaged

myocardium. Autologous cells are preferred in order to reduce the immune response (page 2 para 23-24).

Chachques does not teach the use of autologous human serum, heparin, protamine or the specific concentrations as claimed by Applicant.

Furcht et al teach a method of culturing cardiomyocytes to be used to treat cardiac diseases such as cardiomyopathy (disorder of the myocardium) (column 9 lines 30-34). The cells can either be maintained in the presence of fetal calf serum or autologous serum (column 15 lines 39-41).

Therefore one of ordinary skill in the art would have been motivated to use autologous serum in the culture medium of Chachques given that Chachques emphasizes the importance of avoiding an immune response by using autologous cells and Furcht et al also teaches that cardiac cells can be cultured with autologous serum as well as fetal calf serum. One of ordinary skill in the art would have had a reasonable expectation of success because both Chachques and Furcht et al were culturing cardiac cells for the treatment of a damaged myocardium.

Furcht et al is silent with regard to the method of collecting the autologous serum from the patient.

Duggins teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media (background, column 1 lines 28-32).

Yang et al teach that heparin is a coagulant of choice particularly in all procedures involving extracorporeal blood circulation such as plasmapheresis (background, column 1 lines 25-35). Protamine is used to neutralize the negative side-

effects of heparin and yang et al teach a specific protamine that is bioactive and has low toxitcity (column 3 lines 45-55).

Therefore one of ordinary skill in the art would have been motivated with a reasonable expectation of success to use plasmapheresis to obtain autologous serum for the culture medium of Chachques because Duggins teaches that plasmapheresis is commonly used to obtain serum proteins and to produce cell culture media. One of ordinary skill in the art would have also been motivated to use heparin as the anticoagulant in the plasmapheresis method as Yang et al teach that it is commonly known in the art to do so. One of ordinary skill in the art would have been motivated to use the specific protamines described by Yang et al in the plasmapheresis method as Yang et al teaches that they neutralize the negative side-effects of heparin and are bioactive and have low toxicity. Applicant has disclosed that the use of heparin and protamine in a plasmapheresis method would have provided an autologous serum with roughly the same amounts (or similar) of heparin and protamine in the serum as claimed by Applicant (Specification page 5 para 28). The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

The concentrations of the ingredients in the culture medium would have been a matter of routine optimization and experimentation, the artisan of ordinary skill

recognizing that the growth of the cells and the success of their therapeutic application would be affected by these concentrations and thus be result-effective variables.

Therefore the combined teachings of Chachques, Furcht et al, Duggins and Yang et al render obvious Applicant's invention as claimed.

Claims 31-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (US 6,472,212) in view of Wilson et al (US 5,817,773).

Valerio et al describe methods and compositions for culturing primate bone marrow cells, specifically including human cells (column 26 example d). A media composition is described that comprises a base culture medium that includes basic nutrients, 5% heat inactivated autologous human serum, 4 µg/ml protamine sulfate and 100 U/ml penicillin (column 29 lines 33-40). Many different types of culture media are taught to be suitable and commercially available and a short non-restricted list is mentioned. While Ham-F12 is not on that list, it is a media known in the prior art to be used for culturing bone marrow cells and would have been an obvious alternative. The serum amounts are taught to vary from 5 to 30% and the media compositions are taught to include one or more antibiotics as well as growth factors (column 14 lines 57-63). Streptomycin is indicated as an acceptable antibiotic for inclusion in the media composition with penicillin as well (column 24 line 44).

Valerio et al do not specifically include heparin or fibroblast growth factor (FGF) in the media composition.

Wilson et al teach the stimulation of hematopoietic cells with fibroblast growth factor (FGF). An FGF is also taught to be used in combination with other growth factors (column 12 lines 20-25). Heparin sulfate is taught to be used to potentiate the stimulatory effect of concentrations of an FGF administered to hematopoietic cells (column 12 lines 63-66). Addition of at least one FGF in combination with heparin to a bone marrow cell culture is taught to increase the numbers of stem cells in a population to be used for transplantation (column 17 lines 25-30). Recombinant FGFs are taught to be used as well (column 17 lines 37-62). Low concentrations of bFGF (0.2 ng/ml which is equal to 200 pg/ml) are taught to significantly enhance cell growth (column 22 lines 41-43) especially when combined with low concentrations of heparin.

Therefore one of ordinary skill in the art would have been motivated to add FGF with heparin to the media of Valerio et al because Wilson et al teach that FGF combined with heparin stimulates the growth of bone marrow cells. One of ordinary skill in the art would have had a reasonable expectation of success because both Valerio et al and Wilson et al were culturing bone marrow cells for therapeutic administration to humans.

The concentrations of the FGF and the heparin in the culture medium would have been a matter of routine optimization and experimentation, the artisan of ordinary skill recognizing that the growth of the cells, the success of their therapeutic application and the cost of the procedure would be affected by these concentrations and thus be result-effective variables.

Therefore the combined teachings of Wilson et al and Valerio et al render obvious Applicant's invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA SCHUBERG whose telephone number is (571)272-3347. The examiner can normally be reached on Mon-Fri 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leon B Lankford/
Primary Examiner, Art Unit 1651

Laura Schuberg